

LUNG CANCER

Improved Cytologic Detection by Inducing Production of Sputum

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■ *The principle of producing bronchial lavage by deposition of large amounts of heated aerosol has resulted in a significantly greater yield of positive cytologic diagnosis of bronchogenic carcinoma than with repeated "volunteer" specimens of sputum. Positive pressure plus bronchodilators augments greater sputum volume.*

Using this technique, cases in which results of bronchoscopy and aspiration biopsy were negative for malignant change, were diagnosed cytologically.

Application of this technique can sometimes detect early lung carcinoma before roentgenographic changes are detectable. Positive tests in clinically far advanced disease may prevent unnecessary surgical intervention.

The simplicity of the technique, the freedom from adverse reactions, and its wide acceptance by the subjects tested, make it valuable in the diagnosis of lung cancer.

BRONCHIAL LAVAGE IS produced by deposition of large amounts of heated aerosol together with the condensation of water vapor on the relatively colder surfaces of the respiratory passageways. This is achieved by inhaling an aerosol mist at approximately 125°F, from a volume-producing nebulizer which liquefies retained secretions and aids in their expectoration.²

Factors which determine the degree of retention of an aerosol and the sites of deposition within the respiratory tract are: The particle size and density, vapor pressure, temperature, the hygroscopic properties of the aerosol and the rate and depth of respirations.

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Ninety-seven per cent of solid particles of 1 micron or less are deposited within the lung. Particles of 3 micra in radius are taken out completely by the trachea, the bronchi and the bronchioles. Wilson and La Mer¹⁰ reported maximal retention of approximately 50 per cent in the alveoli and bronchioles with particles of 1 micron in radius.¹⁰

The stability of a water droplet 0.5 micron in radius under ordinary conditions of humidity is only a fraction of a second, due to its high evaporation rate. Furthermore, rapid absorption of isotonic aerosols takes place within the tracheobronchial tree.

Studies by Abramson¹ indicated that droplet evaporation is decreased with aerosols in a gly-

TABLE 1.—*Comparison of Cytologic Diagnosis of Spontaneous and Induced Sputum in Patients with Suspected Pulmonary Malignant Disease*²

	No. of Cases	Positive for Malignant Cells	Suspicious Abnormal Cells	Negative for Malignant Cells
Spontaneous sputum*	14	2	2	6
Induced sputum	14	9	5	

*Four specimens unsatisfactory for cytologic study.

cerin solution, the reduction in vapor pressure serving to stabilize the aerosol mist. Decreased deposition of a mist occurs if the aerosol is heated; also, heating decreases irritation to the respiratory tract and reduces viscosity.

Impingement of an adequate number of hypertonic saline droplets upon the bronchial mucosa will induce transudation by osmosis; such bronchial transudate washes exfoliated cells into the material subsequently expectorated.³

The striking differences in the results obtained with induced sputum as compared with those from spontaneous specimens may perhaps be explained by the following possibilities: (1) Poor preservation of the cells in spontaneous sputum by reason of varying periods of retention within the tracheo-bronchial airway; and, (2) a mixture of saliva and postpharyngeal secretions, producing a "dilution" effect on the bronchial secretions.²

Barach and coworkers² compared methods of spontaneous and induced sputum technique in the same 14 patients suspected of pulmonary malignant disease. A significantly higher yield of malignant cells was obtained with the induced sputum technique (Table 1).

Material and Method

Inhalation of 15 per cent sodium chloride combined with 20 per cent propylene glycol preheated to 160°F is used. The aerosol at the end of the mouthpiece is approximately 110°F to 120°F. The inhalation period is approximately 30 minutes.

At the end of that time a specimen is collected and the patient is handed a sterile specimen flask, containing 95 per cent ethyl alcohol fixative, and is instructed to spit into it all sputum during the ensuing 24 hours.

The use of intermittent positive pressure breathing accomplishes better distribution of air (and aerosol) throughout the lung parenchyma.⁷

In the present series a 1:200 Isuprel solution was introduced into the circuit to enhance bronchial lavage.

Either oxygen or compressed air* can be used for gas flow.

Reports of Cases

CASE 1. An 84-year-old farmer, a non-smoker, had been in good health, except for duodenal ulcer treated in 1959, until an episode of influenza in January of 1963. Cough and shortness of breath developed and an ejection systolic cardiac murmur was noted. The patient was in congestive heart failure and was digitalized. He improved for a few weeks. However, fluid formed in the right pleural space and he subsequently had weight loss and increasing dyspnea. On 17 January 1963, thoracentesis revealed pleural fluid, and a cell button highly suspicious of malignant cells. An x-ray film of the chest subsequent to the thoracentesis revealed no definite mass in the right lung but did show a prominence of the right hilus. Bronchoscopy in January of 1963 with bronchial biopsy revealed no tumor. The histologic diagnosis was chronic bronchitis. On 4 February 1963, an x-ray film showed atelectasis of the right middle lobe with associated soft tissue mass in the lower right hilum and right pleural effusion. On 17 February, a 24-hour voluntary sputum specimen, not induced, was negative for malignant cells. Bronchial washings at the time of bronchoscopy were negative for malignant cells.

On 25 February sputum induction with heated aerosol inhalation revealed atypical suspicious cells present, probably malignant (Class III or IV). A review of previous cytologic studies on pleural fluid showed similar cells present. In consultation a thoracic surgeon concurred with the diagnosis of inoperable lung tumor.

CASE 2. The patient, a 77-year-old white man, a retired citrus orchardist, had smoked 20 cigarettes a day for 40 years. He had been losing weight, had been chronically fatigued and had had shortness of breath on exertion for several months. He complained of chronic cough which he had had for two years, and in recent months he had had pain in the left side of the chest. X-ray

*Mistogen, Temp-trol model CY-2.

studies of the chest demonstrated atelectasis of the left upper lobe and pleural effusion.

Bronchoscopy showed a tumor obstructing the left upper lobe bronchus. This mass was visualized directly by use of an angled mirror.

Pleural fluid submitted for cell button and cytologic studies was reported as negative for malignant cells by the pathologist. The scalene lymph nodes resected from the left were also reported negative. Bronchial washings contained "insufficient cells" for adequate study. A study of a 24-hour specimen of sputum, non-induced, collected by the patient was reported as negative for malignant cells.

The clinical diagnosis was bronchogenic carcinoma, left upper lobe, with atelectasis of the left upper lobe and pleural effusion on the left.

A 24-hour specimen of induced sputum was reported by the pathologist as positive for malignant cells, Class V, squamous.

The tumor was considered inoperable.

CASE 3. The patient, a 54-year-old food handler, who had smoked about 20 cigarettes a day for many years, complained of thoracic discomfort and pain in the back for two months. An x-ray film of the chest showed a cavitating lesion of the left upper lung reported as "most likely carcinoma." This was confirmed by pneumonectomy.

An induced sputum specimen and cell button studies were positive for malignant cells, Class V.

Within two months after pneumonectomy the patient was in a terminal stage of disease with widespread node and bony metastasis.

Patients with cavitory lesions are excellent candidates for screening for malignant disease by the heated aerosolized induced sputum technique.

CASE 4. A 68-year-old man, a painter, complained of a dull ache in the left anterior chest and later cough and hemoptysis. A physician had administered antibiotics with no appreciable effect. The thorax was symmetrical, breath sounds were normal and there were no rales. The heart was of normal size with a regular rhythm and no murmurs. An x-ray film of the chest revealed infiltration of the left lung field and the region of the lingular segment of the upper lobe. This was thought to be due to lobar pneumonia. Results of bronchoscopy were negative and a bronchial biopsy revealed no pathologic change in bronchial

mucosa. Bronchial washings were reported as negative for disease. On biopsy of a scalene node taken from the left side, the morphologic structure was that of a rather anaplastic carcinoma compatible with carcinoma of the lung or of the pancreas.

Examination of sputum induced by heated aerosol inhalation revealed highly atypical cells that, on cell button examination, were suspicious of carcinoma.

Carcinoma of the lung with supraclavicular node metastasis and probably metastasis to the lumbar spine was diagnosed.

Subsequent palliative treatment with 5 fluorouracil, 1 gram daily for six days, followed by local x-ray therapy to the lumbar spine area was given. The condition of the patient deteriorated rapidly.

In this case, earlier resort to a screening test by induced sputum could have prevented an unnecessary scalene node biopsy. This case serves as an example of the usefulness of detecting metastatic lung disease as well as primary lung carcinoma.

CASE 5. The patient, a 59-year-old salesman who had smoked 40 cigarettes a day for many years, had a "chest cold" with a dull aching in the chest above the left breast. Coughing was productive of a tannish exudate and occasional foul green sputum.

On physical examination, dullness to percussion was noted over the left upper lobe posteriorly and anteriorly.

An x-ray film of the chest showed left upper lobe opacification primarily in the area of the apical posterior segment. Bronchial compression or obstruction was considered probable.

Sputum induction with heated aerosol inhalation produced results as follows: First specimen, smears and cell button positive for Class V squamous cells. Second specimen (24 hours), smears positive for Class V squamous cells.

On bronchoscopic examination no tumor could be seen—only purulent sputum exuding from the left main stem bronchus. Scalene nodes were removed from both sides. On gross examination they appeared normal and the specimens were not submitted to the pathologist.

Thoracotomy was carried out a week after the induced sputum examination. On biopsy of the left upper lobe and a mediastinal node a diagnosis

TABLE 2.—*Results of Sputum Examination for Cancer Cells in 77 Patients with Proved Lung Cancer*⁵

Diagnosis	Total Patients	Total Positive	Routine Specimen	Patients with Cancer Cells in Sputum	
				Induced Specimen	
				Total Direct	Delayed Only
Bronchogenic carcinoma	59	33	9*	28	4
Metastatic cancer to the lung.....	18	9	2*	7	1

*Induced specimen negative in one patient but positive in others.

was made of primary bronchogenic squamous cell type carcinoma, inoperable.

In this case, after the induced sputum specimens were positive for squamous cell carcinoma of the lung, subsequent bronchoscopy and scalene node procedures could have been avoided and exploratory thoracotomy carried out.

Discussion

Papanicolaou⁸ reported several instances in which the sputum smear supplied the first evidence of malignant neoplasm. In some cases malignant cells were seen in the sputum smears when results of bronchoscopy and aspiration biopsy were negative. In one case in which three successive aspiration biopsies were negative, the sputum smear was positive and revealed "several abnormal cells offering conclusive evidence of malignancy and slight metaplasia." Subsequent exploratory thoracotomy showed inoperable cancer of the lung.

Farber⁴ discussed the clinical applications of cytologic diagnostic technique and said that it is of value to the thoracic surgeon in establishing a reliable preoperative morphologic diagnosis of lung cancer. A positive cytologic diagnosis may be made in many cases in which, the lesions being located in the periphery of the lung or upper lobe bronchi, bronchoscopic examinations are of limited value. Difficult diagnostic problems may be solved when a definite morphologic diagnosis of cancer is made by positive cytologic studies. In patients with coexistent pulmonary tuberculosis and bronchogenic carcinoma, cytologic studies may clarify confusing clinical symptoms.

Cytologic studies of sputum may be utilized as routine screening procedures on patients with minimal or no pulmonary symptoms.

In Farber's series of pathologically proven bronchogenic cancer, a positive cytologic diagnosis was made oftener and sooner than was diagnosis by morphologic studies. In 47 per cent of these cases cytologic examination was the first diagnostic procedure to establish a morphologic diagnosis.

Fontana and coworkers⁵ used the induced spu-

tum technique in 201 cases in which cancer was suspected. Of the 77 patients subsequently proven to have lung cancer, 40 (52 per cent) had cancer cells in induced sputum specimens. Induced sputum specimens were positive for cancer cells in eight of 18 patients with proven metastatic cancer to the lung (Table 2).

Umiker and coworkers⁹ used the heated aerosol technique after "volunteer" sputum had already been examined, and thereby increased the positive cytologic diagnosis of cancer of the respiratory tract from 68.8 per cent to 87.5 per cent in a group of 32 histologically proven cases. Then, on repeated induction, 96.9 per cent of the patients had positive or suspicious smears.

Since the procedure for inducing sputum is not a demanding one, patients readily accept it and usually have no objection to repeating it if additional studies seem advisable. As the criteria for establishing the diagnosis are well established, the number of false positive and false negative reports is kept to a minimum. Bronchial epithelial cells and alveolar phagocytes identify the source of the specimens.

Carcinoma of the lung can sometimes be discovered by cytological examination of sputum before roentgenographic changes are detectable.⁶ The lesions in such instances are usually small, centrally located, epidermoid, bronchial carcinomas hidden by mediastinal or hilar shadows; or they may still be in situ or only superficially invasive.

Experience with this technique is still limited, but it would appear to have value for screening all adult patients with respiratory symptoms or signs and those in whom the risk of lung cancer is increased by age and heavy smoking or by previous oral or laryngeal carcinoma. The use of induced sputum for diagnosis may save the patient with advanced and inoperable lung cancer needless surgical procedures.

It is believed earlier diagnosis will be made when cytologic techniques are applied immediately after cancer is suspected and when this diagnostic

method is utilized on patients with equivocal lung lesions detected by routine roentgen surveys. Also, when patients with cough and sputum—whether cancer is suspected or not—are routinely studied by cytologic techniques.

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